REMARKS

Amendments to the Claims

Claim 1 has been amended and new claims 18 and 19 added to recite preferred embodiments of applicants invention that are even further removed from the prior art.

Claim 1 has been amended to delete the phrase "*method including the step of preparing the …….. by incorporating therein*". The method now comprises administering to the said human a composition capable of inhibiting glucocorticoid-induced chronic stress ….. said composition comprising…….

Claim 1 has been further amended to specify that the composition inhibits glucocorticoid-induced chronic stress in a specific in vitro assay (page 2, lines 1-4) which comprises the following steps (i)-(iv) which are disclosed on page 4, line 23 to page 5, line 2 and described in detail in examples 1-2:

(i) contacting a dermal cell or a cell involved in skin inflammatory responses with the composition in the presence of a glucocorticoid receptor agonist under conditions and for a period of time that would, in the absence of the candidate first and second substance, lead to the cell being chronically stressed (page 4, lines 23-26);

(ii) subjecting the cell to acute stress (page 4, line 27);

(iii) analysing one or more cellular markers selected from a marker of inflammatory cell recruitment, where the cell is a cell involved in skin inflammatory responses; a marker of matrix degradation, where the cell is a dermal cell; and/or a marker of matrix synthesis in the cell, where the cell is a dermal cell (page4, line 28-32);

(iv) determining whether the composition affects the status of the one or more cellular markers (page 5, lines 1-2).

New claim 18 recites a method of reducing the effects of neuroendocrine-mediated, psychologically-induced stress on the skin of a human *desiring to reduce phycologically-induced stress on their skin.* Support for this preamble is provided in the language on page 1, lines 13-14 and especially page 2, lines 15-19 and original claim 1 which is directed to the use of the recited compounds for the manufacture of composition specifically designed for use by individuals to reduce phycologically-induced stress on skin.

The method comprises administering to the individual a composition capable of inhibiting glucocorticoid-induced chronic stress in a dermal cell or a cell involved in skin inflammatory responses, said composition comprising, a first substance selected from the group consisting of ginsenoside Rb1, ginsenoside Rc, curcumin, 22-OH-cholesterol, ciglitazone, mevinolin, commipheric acid, okadaic acid, liquorice extract and mixtures thereof; and a second substance selected from the group consisting of wolfberry extract, shiitake extract, activin, ginseng Rbl, ginseng Rc, curcumin, ciglitazone, commipheric acid, boswellia extract and mixtures thereof, provided that said first substance and second substance are different (page 2, lines 9-13 and page 3, lines 11-18).

New claim 19 specifies that the composition recited in claim 18 inhibits glucocorticoid-induced chronic stress in an in vitro assay (page 2, lines 1-4) which comprises the following steps (i)-(iv) which are disclosed on page 4, line 23 to page 5, line 2 and described in detail in examples 1-2:

(i) contacting a dermal cell or a cell involved in skin inflammatory responses with the composition in the presence of a glucocorticoid receptor agonist under conditions and for a period of time that would, in the absence of the candidate first and second substance, lead to the cell being chronically stressed (page 4, lines 23-26);

(ii) subjecting the cell to acute stress (page 4, line 27);

(iii) analysing one or more cellular markers selected from a marker of inflammatory cell recruitment, where the cell is a cell involved in skin inflammatory responses; a marker of matrix degradation, where the cell is a dermal cell; and/or a marker of matrix synthesis in the cell, where the cell is a dermal cell (page4, line 28-32);

(iv) determining whether the composition affects the status of the one or more cellular markers (page 5, lines 1-2).

Claims Objections

The objection to claim 17 is rendered moot since the claim has been canceled.

Claims Rejection under 35 USC §103

Claims 1-7 and 16 were rejected under 35USC §103(a) as being unpatentable over Shefer et al (US 2003/0232091 – hereinafter "Shefer"). Applicants respectfully traverse this rejection.

Shefer is directed to a controlled release system useful in stabilizing retinol, retinol derivatives, and extracts containing retinol in cosmetic, dermatological, and pharmaceutical compositions. Shefer teaches stabilized retinol in a solid hydrophobic particle that sustains the release of retinol during the product shelf life and enables a gradual and prolonged release of effective levels of retinol and other cosmetic, dermatological, and pharmaceutical active ingredients into biological surfaces.....The invention further relates to cosmetic, dermatological, and pharmaceutical products comprising stable retinol in a hydrophobic particle that can deliver effective levels of retinol and other cosmetic, dermatological, and pharmaceutical active ingredients to biological surfaces over an extended period of time (Abstract).

Shafer teaches *many hundreds* of optional "Active Ingredients" selected among *21 different functional classes* that can be included in the capsule composition.

Shafer mentions gensenoside Rc, circumin, and licorice among the *400+* materials listed under the functional class "Non-steroidal Cosmetic Soothing Actives" on pages 9 and10, [106] - [107].

Shafer is silent regarding any method related to reducing the chronic effects of neuroendocrine mediated psychologically-induced stress on the skin. The only reference to "stress" found in the entire reference is a statement that "valerian tincture, extracts of melissa and hop may be used to cause a sedative effect in case of superexcitation, sleep disturbances, and *stress"* (page 13, [0135]).

Just because one could have constructed the combination recited in current claim 4 by combing various optional or alternative materials disclosed in a reference is no reason to do so.

Shefer, provides no teaching or suggestion that would have even remotely directed a person of ordinary skill in the art to have chosen a combination that included at least two of gensenoside Rc, circumin, and licorice from the list of 400+ compounds *recited alphabetically* in paragraph 107. Not even one of the compounds recited in the *entire list* of 400 is included in any of exemplary compositions taught by Shefer.

Applicants further point out that the list of 400 soothing agents also includes rosemary and an extract of pine bark. Applicants have tested both ingredients and found them to be ineffective in inhibiting glucocorticoid-induced chronic stress (Specification - table 2 page 39). Thus, the list does not provide any basis beyond random chance for selecting materials that are effective in inhibiting glucocorticoid-induced chronic stress.

Applicants' respectfully submit that it is only through hindsight using applicants' disclosure as a blueprint could the combination of gensenoside Rc, circumin, and licorice be considered as having been obvious to a person of ordinary skill in the art even for the purposes disclosed by Shefer, e.g., to be incorporated into retinol capsules, let alone for the treatment of glucocorticoid-induced chronic stress.

Furthermore, even in the extremely remote possibility that gensenoside Rc, circumin, and licorice were randomly selected from the list of 400 compounds, Shefer provides no guidance as to how the amount should be selected so that the composition would be capable of reducing the chronic effects of neuroendocrine mediated psychologically-induced stress on the skin. Shafer is completely silent about the entire subject of neuroendocrine-mediated psychologically-induced stress on the skin, let alone providing an in-vitro method to test compositions for their ability to inhibit glucocorticoid-induced chronic stress.

The Examiner asserted that it would have been obvious at the time of the invention to administer a composition to an individual based on its anti-inflammatory properties for skin care. Although this may apply to some types of dermatological conditions, it is certainly not true for compositions designed for reducing *glucocorticoid-induced chronic stress* on skin. Applicants have demonstrated the surprising and unexpected result set forth in Table 2 on page 39 that just because an agent has anti-inflammatory properties does not ensure its effectiveness in inhibiting glucocorticoid-induced chronic stress in either a dermal cell or a cell involved in skin inflammatory responses. For example, applicants have demonstrated that the anti-inflammatory agents Resveratrol and WY14643 are both ineffective in inhibiting glucocorticoid-induced chronic stress (Table 2, page 39).

In summary, Shefer is directed to the problem stabilizing retinol in skin care compositions. This is very different from applicants' method directed to the problem of reducing the effects of neuroendocrine-mediated, psychologically-induced stress on skin. Shefer makes no reference to this problem or anything remotely related to it. The

Examiner's selection of three of the compounds recited in claim 4 from among the hundreds of optional ingredients recited by Shefer is purely based on hindsight and, moreover, absent a disclosure of the in vitro test method to insure the cabability of inhibiting glucocorticoid-induced chronic stress, Shefer does not present a *prima facie* case of obviousness over applicants' claims.

Claims 16 is even further removed from Shefer because its recites an additional limitations not taught or suggested by Shefer, namely that the composition recited in the method of claim 4 is capable of inhibiting both glucocorticoid-induced chronic stress in a dermal cell and glucocorticoid-induced chronic stress in a cell involved in skin inflammatory responses. Shefer is silent regarding the inhibition of glucocorticoid-induced chronic stress, let alone inhibiting it in both a dermal cell and a cell involved in skin inflammatory responses, e.g., endodermal cells.

In view of the above amendments and remarks, applicants respectfully request that the §103(a) rejection over Shefer et al be reconsidered and withdrawn

Regarding claims 17 and 18

Applicants reiterate that Shefer is directed to the problem stabilizing retinol in skin care compositions. This is very different from applicants' method directed to the problem of reducing the effects of neuroendocrine-mediated, psychologically-induced stress on the skin of individuals desiring such improvements. Shefer makes no reference to this problem or anything remotely related to it.

Applicants' have shown in their examples the unpredictable effects of components in reducing glucocorticoid-induced chronic stress, e.g., that anti-inflammatory properties does not ensure effectiveness in reducing glucocorticoid-induced chronic stress. Applicants' have further shown that some of the compounds disclosed by Shefer, i.e., rosemary and extract of pine bark, are ineffective in reducing glucocorticoid-induced chronic stress even though they are taught by Shafer to be suitable materials.

Thus, applicants' respectfully submit that Shafer et al would have provided the skilled person with neither the insight nor direction to develop a method for reducing the effects of neuroendocrine-mediated, psychologically-induced stress on individuals desiring such improvements, let alone the specific compositions recited in claim 17 and the in-vitro test methods recited in claim 18.

In light of the above amendments and remarks, applicants respectfully request that the application be allowed to issue as a patent.

In the event any questions remain, the Examiner is kindly invited to contact the undersigned agent at her earliest convenience.

Respectfully submitted,

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